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ABSTRACT:

PURPOSE: To obtain an immunosuppressive agent which is employed in a sustained release preparation and can be effectively migrated into the lymphducts depending to its desired releasing properties, when it is embedded in a body very close to the duct.

CONSTITUTION: This embedding sustained release immunosuppressive preparation comprises 100 pts.wt. of an aliphatic polyester which is absorbable in vivo, 1-200 pts.wt. of a nonionic surfactant and 0.1-100 pts.wt. of a lipid-soluble immunosuppressive agent.

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**(54) EMBEDDING SUSTAINED RELEASE
IMUNOSUPPRESSIVE AGENT**

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Abstract

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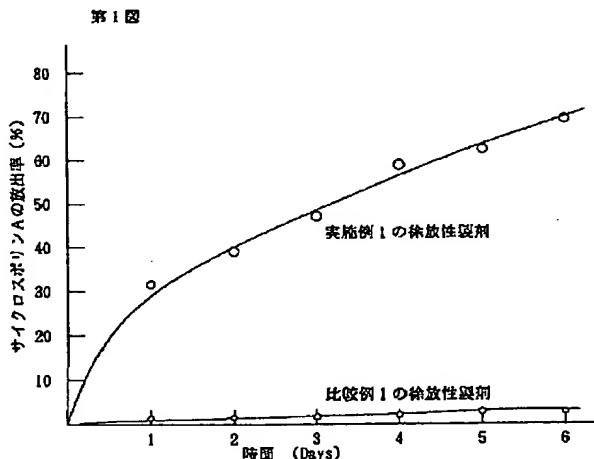
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(54) 【発明の名称】埋込型徐放性免疫抑制剤

(57) 【要約】

【構成】 生体吸収性脂肪族ポリエステル100重量部に対して、非イオン性界面活性剤を1~200重量部及び脂溶性の免疫抑制薬を0.1~100重量部を含有させてなる埋込型徐放性免疫抑制剤。

【効果】 リンパ管に密接して埋め込むことによって、徐放性製剤中の免疫抑制薬をリンパ管へ、効果的に、かつ所望の徐放特性に応じて移行させることができる。



【特許請求の範囲】

【請求項1】 生体吸収性脂肪族ポリエステル100重量部に対し、非イオン性界面活性剤を1～200重量部及び脂溶性の免疫抑制薬を0.1～100重量部を含有させてなる埋込型徐放性免疫抑制剤。

【請求項2】 生体吸収性脂肪族ポリエステルが、ポリグリコール酸、ポリ乳酸およびグリコール酸-乳酸共重合体から選ばれた脂肪族ポリエステルである請求項1記載の徐放性免疫抑制剤。

【請求項3】 免疫抑制薬が、サイクロスボリンである請求項1記載の徐放性免疫抑制剤。

【発明の詳細な説明】

【0001】

【産業上の利用分野】 本発明は、生体内において所望の徐放特性を示す脂溶性免疫抑制薬の埋込型の徐放性製剤に関する。より詳細には、脂溶性の免疫抑制薬および非イオン性界面活性剤を生体吸収性脂肪族ポリエステルに含有させてなる埋込型徐放性製剤に関する。

【0002】

【従来の技術】 サイクロスボリン、アゼチオプリン、ブレドニゾロンなどの免疫抑制剤は、臓器移植時の拒絶反応を抑止する。これらの免疫抑制剤はリンパ系に存在する免疫担当細胞群に直接働きかけ、殺細胞的あるいは機能損傷により免疫機能の低下を果たす。これらの薬剤は、従来、注射剤または経口剤として投与されているが、2つの大きな問題点があった。すなわち、一つに一定期間連続投与が望ましいのにもかかわらず投与量の安全域が狭く、過量では骨髄抑制、腎機能障害を引き起こし、不足量では効果が十分に発現されないこと、二つに、従来の投与方法ではリンパ系への移行が悪く効果が十分でなく、かつ他器官での濃度が上昇し副作用を誘導していた。

【0003】 このような問題点を改善するため、従来、これらの脂溶性薬剤がオリーブ油やゴマ油等に分散させた油性製剤として使用されていたものを、界面活性剤を用いて水中に分散させた薬剤として経口投与し、消化管からの吸収を促進し、かつリンパ指向性を著しく向上させる提案がある(特開昭61-280435)。また、これらの薬剤を医学的に許容される有機溶媒可溶界面活性剤と常温で固体の有機溶媒可溶性物質と緊密に混合した溶解性粉末状製剤の提案もされている(特開昭64-38029)。上記の免疫抑制薬の問題点から、免疫抑制薬の効果的な投与方法としては、リンパ系への移行率が高く、かつ一定期間一定濃度以上に薬剤を放出する高密度に放出抑制された徐放性製剤が望ましい。

【0004】 徐放性製剤として、生体吸収性脂肪族ポリエステルを基材としてこれに薬剤を含有させたものが開発されている。生体吸収性脂肪族ポリエステルは、ポリグリコール酸、ポリ乳酸、グリコール酸-乳酸共重合体及びこれらの組成物であり、これらの脂肪族ポリエス

テルは生体内で無害なものとして分解、吸収処理ないし排出されるので薬剤の基材として好適である。これらの材料を薬剤の基材として使用するときに要求される特性としては、生体親和性、生体内分解性等の外、薬剤等を含浸した材料については一定期間内に薬剤を基材から放出するという徐放制御性が重視されている。

【0005】 すなわち、生体吸収性脂肪族ポリエステルと薬剤とのみから構成されるだけでは、薬剤の放出が治療効果に合わない場合があり、薬剤の放出特性を治療目的に合わせて調整された徐放性製剤の開発が、薬剤の化学的物性に合わせて、また治療目的に合わせて、きめ細かく、かつ厳密に行われている。このような生体吸収性脂肪族ポリエステル、脂溶性添加物および薬剤とからなる顆粒状に調製された徐放性製剤が提案されている(例えば、特開昭58-065211号、特開昭61-063613号)。

【0006】 この徐放性製剤は、生体吸収性脂肪族ポリエステルと薬剤とからなる顆粒状の徐放性薬剤の徐放性を向上させるように改善されたものであり、このマイクロスフェアを血液中に供与してマイクロスフェアから薬剤を徐放させる方法で薬効を一定期間保とうとするものである。しかしながら、免疫抑制剤について、リンパ系への移行効果が十分な投与方法や、安全領域の投与量で一定期間連続投与ができる徐放性製剤の開発は未だなされていない。

【0007】

【発明が解決しようとする問題点】 本発明の課題は、免疫抑制剤のリンパ系への移行が効果的で、かつ所望期間・所望濃度範囲で薬剤を徐放できる、高度に徐放特性が抑制された徐放性免疫抑制剤を提供することである。本発明者は、これらの課題を解決するため鋭意検討した結果、生体吸収性脂肪族ポリエステルに非イオン性界面活性剤と免疫抑制剤からなるマトリックスを、胸腺部分に密接できる形状に成形して、埋め込むことにより、免疫抑制剤の放出を所望の徐放特性に調整し、かつ効率的にリンパ系中に移行できることを見出し、本発明を完成するに至った。

【0008】 すなわち、本発明は、生体吸収性脂肪族ポリエステル100重量部に対し、非イオン性界面活性剤を1～200重量部及び脂溶性免疫抑制剤を0.1～100重量部を含有させて成形した埋込型徐放性免疫抑制剤である。この本発明の徐放性免疫抑制剤は、脂溶性免疫抑制剤と生体吸収性脂肪族ポリエステルの基材にさらに非イオン性界面活性剤を添加したマトリックスとしたところに特徴があり、さらに、特定の器官に合わせて成形した埋込型徐放性製剤であり、これを特定器官に密接して埋め込み、リンパ系中に移行を効果的にかつ徐放時間を制御できるようにしたところに特徴がある。

【0009】

【課題を解決させる手段】 本発明は、生体吸収性脂肪族

ポリエステル、非イオン性界面活性剤及び脂溶性免疫抑制薬からなるマトリックスを成形した徐放性製剤である。本発明に用いられる非イオン性界面活性剤とは、医学的に許容される非イオン性界面活性剤で、グリセリン脂肪酸エステル、ポリグリセリン脂肪酸エステル、ポリオキシエチレンソルビタン脂肪酸エステル、ポリエチレングリコール脂肪酸エステル、ポリオキシエチレンヒマシ油、硬化ヒマシ油、ポリオキシエチレン、アルキルエーテル、ポリオキシエチレンポリオキシプロピレンアルキレンエーテルなどが挙げられる。特にポリオキシエチレンヒマシ油、硬化ヒマシ油が好ましい。

【0010】使用する非イオン性界面活性剤の使用量は、免疫抑制薬の種類、投与形態にもとづく放出速度量により適宜決められるが、通常、生体吸収性ポリエステル100重量部に対して1~200重量部、好ましくは、10~100重量部である。一般に非イオン性界面活性剤の使用量は、免疫抑制薬の放出特性を短期間に、高く設定した場合は、使用量を多くし、逆の場合は、使用量を少なくする。本発明に用いられる生体吸収性脂肪酸ポリエステルとは、ポリ-L-乳酸、ポリ-DL-乳酸または乳酸-グリコール酸の共重合物であり、ポリL-乳酸の場合は、分子量10,000~200,000のものが好ましく、また、ポリ-DL-乳酸の場合は固有粘度0.6~1.2(クロロホルム中、25°Cで測定)程度のものが好ましい。

【0011】本発明に用いられる脂溶性免疫抑制薬とは、リンパ系中でリンパ系に存在する免疫担当細胞群の免疫機能を低下させうる薬効を有するものであり、脂溶性の免疫抑制薬である。例えば、サイクロスボリン、アザチオプリン、プレドニゾロンなど免疫抑制薬が挙げられる。これらの脂溶性免疫抑制薬は、生体吸収性脂肪酸ポリエステル100重量部に対して、0.1~100重量部の範囲で含有させる。

【0012】本発明の埋込型徐放性免疫抑制剤とは、上記の非イオン性界面活性剤、生体吸収性脂肪酸ポリエステルおよび脂溶性免疫抑制薬を上記の使用量の範囲で混合したマトリックを用いて固形状に成形したものである。その形状は、免疫担当細胞の産生に関与するリンパ系の器官である胸腺に密着して埋め込むことが可能な大きさ、形状であればとくに限定されず、板状、半円筒状、フィルム状が好ましい。このような本発明の徐放性免疫抑制剤は常法に従い調製できる。例えば、所望量の生体吸収性脂肪族ポリエステル及び非イオン性界面活性

剤を塩化メチレンなどの有機溶剤に完全に溶解し、この溶液にさらに免疫抑制薬を添加して溶解し、得られた溶液を適当な形状の成形器に入れて溶剤を蒸発除去することにより埋込型徐放性製剤を得る。

【0013】

【実施例】

【実施例1】グリコール酸-乳酸(クロロホルム中25°Cで測定した固有粘度 $[\eta] = 0.50$ を有する)50:50の重合体50mgをビーカ中で攪拌しながら塩

10 化メチレン15gに溶解した後、ポリオキシエチレン硬化ヒマシ油、HCO-60(日光ケミカルズ製、HLB=14)を75mg及びサイクロスボリンA(サンド社製)10mgを加えて溶液を得た。この溶液の一部を、テフロンチューブ(2mm×15mm)を円の中心線に沿って切った半円筒状の型に流し込み、室温で減圧乾燥して4半分の1円筒状(2mmφ×15mm)の成型物を25mgを得た。

【0014】【比較例1】HCO-60を加えないこと以外は、実施例2と同様な手順で4半分の1円筒状の成型物25mgを得た。

【0015】【実施例2】実施例1および比較例1のそれぞれをそのまま用いて溶出試験を行った。それぞれをTween 80 0.5%含有の50mlの生理食塩に入れ、各測定時に直接1~3mlをサンプリングし、210nmにおける吸光度を測定した。これらの吸光度より計算して求めた経過時間と放出率との関係を第1図に示す。

【0016】【参考例1】実施例1および比較例1でそれぞれ得られた埋込型徐放性製剤を用いラットにおける心臓移植後の生着期間に対する効果を調べた。10匹のWistarラットを2群に分け(各群5匹)、Buffaloラットの心臓を、全てのラットの腹腔内に異所性に移植した。ついで、各グループのラットに次の処置を施した。

グループ1: 比較例1の埋め込み剤を胸腺に密着する様に手術用縫合糸を用いて固定した。同時にサイクロスボリンA 5mg/kgを静注した。

グループ2: 実施例1の埋め込み剤を胸腺に密着する様に手術用縫合糸を用いて固定した。同時にサイクロスボリンA 5mg/kgを静注した。

40 各群の生着期間を観察し、その結果は第1表の通りであった。

【表1】

第1表

ラットグループ	生着期間(日)	平均生着期間(日)
1	7, 7, 7, 8, 9	7.6±0.9
2	10, 16, 21, 22, 36	21.0±9.6

この結果、比較例1のHCO-60を用いていない製剤 50 では、サイクロスボリンAの放出が促進されず、免疫機

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能が抑制されず生着期間（日）が短く、これに対してHCO-60を用いた本願の埋込型徐放性製剤は、サイクロスボリンAが第1図に示すような徐放特性に高められて、生着期間（日）が長く、その効果が顕著である。

【0017】

【作用、及び発明の効果】生体吸収性脂肪族ポリエステル、非イオン性界面活性剤及び脂溶性免疫抑制薬を含有してなる本発明の埋込型徐放性免疫抑制剤は、その調製時において、生体吸収性脂肪族ポリエステルに添加された非イオン界面活性剤が、免疫抑制薬を溶解したマトリックスを形成し、薬剤の析出がない。この均質に溶解したマトリックスは、リンパ系内、特に胸腺部分に密着するような埋込形状に成形し、リンパ管の器官に密接して埋め込むことによって、徐放性製剤中の免疫抑制薬をリンパ管へ効率的に、かつ所望の徐放性特性に応じて移行させることができる。

【0018】徐放性製剤に用いる非イオン性界面活性剤の種類とその使用割合を適宜選択することにより、薬物

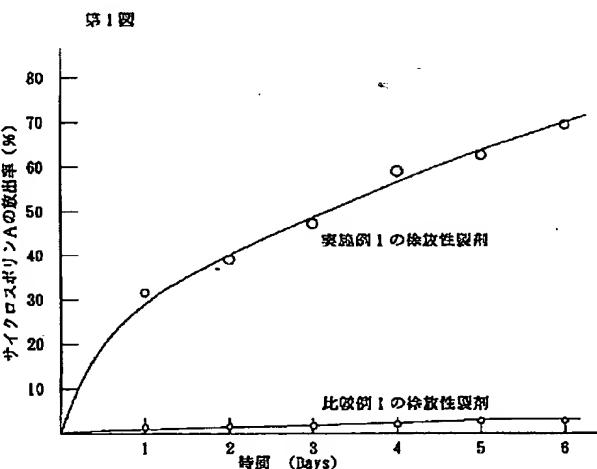
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の徐放時間、徐放量、すなわち徐放速度が所望により制御でき、生体吸収性ポリエステル自体の徐放性とあいまって、薬剤の徐放性が適度に調節できる。徐放された後も非イオン性界面活性剤の吸収促進作用により胸腺、リンパ管に容易に透過されて、作用部位における濃度を一定に保持でき、免疫抑制薬のリンパ管内での薬理効果を適切に維持し十分に発現できる。また、本願の埋込型徐放性免疫抑制剤を使用することにより、従来の注射や経口的に供与する方法にくらべ、骨髄抑制、腎機能障害を引き起こすのを抑制することができる。また、生体吸収性脂肪族ポリエステルは加水分解されるため体外に取り出す必要もなく、体内に残留もしない。すなわち、本願の徐放性製剤は、医学の分野に大きく貢献する製剤である。

【図面の簡単な説明】

【図1】実施例1で得られたサイクロスボリンAを含有する徐放性製剤の、サイクロスボリンAの放出率と時間の関係を示す。

【図1】



ABSTRACT

The present invention provides an implantable sustained release immunosuppressive drug comprising 1 to 200 parts by weight of a nonionic surfactant and 0.1 to 100 parts by weight of a fat-soluble 5 immunosuppressive agent combined with 100 parts by weight of a bioabsorbable aliphatic polyester. When implanted in such a manner that it is brought into intimate contact with a lymph duct, the sustained-release preparation of the present invention can effectively transfer the immunosuppressive agent in the preparation into the lymph 10 duct according to a desired sustained release profile,

WHAT IS CLAIMED IS:

1. An implantable sustained release immunosuppressive drug comprising 1 to 200 parts by weight of a nonionic surfactant and 0.1 to 100 parts by weight of a fat-soluble immunosuppressive agent combined with 100 parts by weight of a bioabsorbable aliphatic polyester.
2. A sustained release immunosuppressive drug of claim 1 wherein the bioabsorbable aliphatic polyester is an aliphatic polyester selected from polyglycolic acid, polylactic acid, and glycolic acid-lactic acid copolymers.
3. A sustained release immunosuppressive drug of claim 1 wherein the immunosuppressive agent is cyclosporin.

DESCRIPTION

Implantable Sustained Release Immunosuppressive Drug

THE FIELD OF THE INVENTION

The present invention relates to an implantable sustained release preparation of a fat-soluble immunosuppressive agent which exhibits a desired sustained release profile *in vivo*. More specifically, it relates to an implantable sustained release preparation which comprises a fat-soluble immunosuppressive agent and a nonionic surfactant combined with a bioabsorbable aliphatic polyester.

10 BACKGROUND ART

Immunosuppressive agents such as cyclosporin, azathioprine, and prednisolone suppress rejection in organ transplantations. These immunosuppressive agents directly act on immunocompetent cell populations existing in the lymphatic system and cause suppression of immunological functions by killing the cells or impairing their functions. Although such agents are conventionally administered as injectables or oral drugs, there have been two major problems as follows. First, in spite of the fact that it is desirable to administer the agents continuously during a certain period, they have a narrow margin of safety, and overdoses cause myelosuppression and/or renal

dysfunction, while underdoses do not produce sufficient effect.

Secondly, the agent is so poorly transferred by conventional methods of administration into the lymphatic system that its effects are insufficient and increased concentrations of the agent in other organs induce side effects.

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In order to address such problems, it has been proposed that, instead of using these fat-soluble agents as an oil-based preparation as before, for example, as a dispersion in olive oil, sesame oil, or the like, they should be orally administered as a drug in which the agent is dispersed in water using a surfactant, to facilitate their absorption from the gastrointestinal tract and to greatly enhance their lymphotropism

(Japanese Patent Publication (Tokkaisho) No. 280435/1986).

Alternatively, a soluble powder preparation has also been proposed in which the agent is intimately mixed with a medically acceptable surfactant soluble in an organic solvent and an organic solvent-soluble substance solid at ordinary temperature (Japanese Patent Publication (Tokkaisho) No. 38029/1989). In light of the above problems associated with immunosuppressive agents, a highly controlled sustained release preparation which provides a high transfer rate into the lymphatic system and releases the agent in such a manner that the

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concentration of the agent is maintained at a certain level or more during a certain period is desirable as an effective method of administering immunosuppressive agents.

A sustained release preparation has been developed which

5 comprises a pharmacological agent combined with a bioabsorbable aliphatic polyester as a base. Bioabsorbable aliphatic polyesters are polyglycolic acid, polylactic acid, glycolic acid-lactic acid copolymers and compositions thereof, and they are suitable as a base for a pharmacological agent, since these aliphatic polyesters are degraded *in vivo* into harmless products and absorbed into or excreted from the

10 body. In the cases where such material is to be used as a base for a pharmacological agent, properties required are, for example, biocompatibility and *in vivo* degradability, and especially for a material impregnated with a pharmacological agent or the like, controlled

15 release properties which allow the agent to be released from the base within a certain period are also regarded as important.

Specifically, since preparations simply comprised of a bioabsorbable aliphatic polyester and a pharmacological agent may not release the agent in a manner that meets requirements for producing a

20 desired therapeutic effect, a sustained release preparation of which

release profile is adapted to its therapeutic goal is developed in a careful and strict way according to the chemical properties of the agent and to the therapeutic goal. Such sustained release preparations formulated in the form of granules which comprise a bioabsorbable 5 aliphatic polyester, fat-soluble additives, and a pharmacological agent have been proposed (e.g. Japanese Patent Publication (Tokkaisho) Nos. 065211/1983 and 063613/1986).

These sustained release preparations have been improved so as to refine the sustained release profile of granular sustained release 10 preparations which comprise a bioabsorbable aliphatic polyester and a pharmacological agent, and these microspheres are intended to be used for maintaining the drug effect during a certain period by introducing them into blood and allowing the agent to be gradually released from the microspheres. For immunosuppressive agents, however, any 15 administration method which provides sufficient transfer of the agent into the lymphatic system, or any sustained release preparation which enables us to continuously administer the agent at a dose in the safety range during a certain period has not yet been developed.

PROBLEM TO BE SOLVED BY THE INVENTION

20 An object of the present invention is to provide a sustained

release immuno suppressive drug having highly controlled sustained release profile which provides effective transfer of the immuno suppressive agent into the lymphatic system and are capable of gradually releasing the agent to give a desired concentration range

5 during a desired period. The present inventors concentrated their efforts on solving these problems and found that release of an immuno suppressive agent can be adjusted so as to have a desired sustained release profile and the agent can also be efficiently transferred into the lymphatic system by molding a matrix comprising a

10 bioabsorbable aliphatic polyester, a nonionic surfactant, and an immuno suppressive agent into a shape capable of intimate contact with thymus and implanting the shaped article. The present invention has been completed based on this finding.

Thus, the present invention is a molded implantable sustained

15 release immuno suppressive drug comprising 1 to 200 parts by weight of a nonionic surfactant and 0.1 to 100 parts by weight of a fat-soluble immuno suppressive agent combined with 100 parts by weight of a bioabsorbable aliphatic polyester. The sustained release immuno suppressive drug of the present invention is characterized in

20 that the matrix comprises a fat-soluble immuno suppressive agent and a

bioabsorbable aliphatic polyester as a base along with a nonionic surfactant further added thereto, and is also characterized in that it is an implantable sustained release preparation molded into a shape adapted to a specific organ such that when implanted in intimate 5 contact with the specific organ, the molded article allows effective transfer of the agent into the lymphatic system and also allows to control the duration of sustained release.

MEANS FOR SOLVING PROBLEM

The present invention is a sustained release preparation 10 prepared by molding a matrix comprising a bioabsorbable aliphatic polyester, a nonionic surfactant, and a fat-soluble immunosuppressive agent. A nonionic surfactant used in the present invention is a medically acceptable nonionic surfactant and examples are glycerin fatty acid esters, polyglycerin fatty acid esters, polyoxyethylene 15 sorbitan fatty acid esters, polyethylene glycol fatty acid esters, polyoxyethylene castor oil, hydrogenated castor oil, polyoxyethylene, alkyl ethers, polyoxyethylene polyoxypropylene alkylene ethers, and the like. In particular, polyoxyethylene castor oil and hydrogenated castor oil are preferred.

20 Although the amount of the nonionic surfactant to be used is

appropriately determined taking into account the type of the immunosuppressive agent and the release rate dependent on the mode of administration, it is usually from 1 to 200 parts by weight and preferably from 10 to 100 parts by weight in relation to 100 parts by 5 weight of the bioabsorbable polyester. In general, the amount of the nonionic surfactant used should be increased in the cases where the release profile of the immunosuppressive agent is to be such that the agent is released at a high concentration in a short period, and the amount should be decreased in the opposite cases. A bioabsorbable 10 fatty acid polyester used in the present invention is poly-L-lactic acid, poly-DL-lactic acid, or a lactic acid-glycolic acid copolymer. Preferably, the poly-L-lactic acid has a molecular weight in the range of 10,000 to 200,000, and for poly-DL-lactic acid, an intrinsic viscosity is preferably about 0.6 to 1.2 (measured at 25°C in chloroform). 15 A fat-soluble immunosuppressive agent used in the present invention is an agent that has a beneficial effect on the lymphatic system which can suppress immunological functions of immunocompetent cell populations existing in the lymphatic system. Examples of immunosuppressive agent include cyclosporin, 20 azathioprine, and prednisolone. These fat-soluble immunosuppressive

agent are combined with 100 parts by weight of a bioabsorbable fatty acid polyester at an amount in the range of 0.1 to 100 parts by weight.

An implantable sustained release immunosuppressive drug of the present invention is a drug molded into a solid form using a matrix 5 in which a nonionic surfactant, a bioabsorbable fatty acid polyester, and fat-soluble immunosuppressive agent described above are mixed at respective amounts described above. Although the shape of the drug is not specifically restricted as long as it has dimensions and a shape which allow the drug to be implanted in intimate contact with thymus, a 10 lymphatic organ involved in production of immunocompetent cells, drugs in the form of plate, half-cylinder, or film are preferred. Such sustained release immunosuppressive drugs of the present invention may be prepared according to the usual methods. For example, 15 desired amounts of a bioabsorbable aliphatic polyester and a nonionic surfactant are completely dissolved in an organic solvent such as methylene chloride, and to the solution thus obtained, an immunosuppressive agent is further added. The resulting solution is then poured into a die having an appropriate shape and the solvent is evaporated off to yield an implantable sustained release preparation.

20 EXAMPLES

Example 1

In a beaker, 50 mg of a copolymer of 50:50 glycolic acid-lactic acid (having a intrinsic viscosity $[\eta] = 0.50$ measured at 25°C in chloroform) was dissolved with stirring in 15 g of methylene chloride, and 75 mg of HCO-60 (a polyoxyethylene hydrogenated castor oil manufactured by Nikko Chemicals; HLB=14) and 10 mg cyclosporin A (Sandoz) were then added to give a solution. An aliquot of the solution was poured into a half-cylindrical die prepared by cutting a Teflon tube (2 mm x 15 mm) along with the centerline of the circle, and 10 dried under reduced pressure at room temperature to yield a quarter-cylindrical (2 mm φ x 15 mm) molded article having a weight of 25 mg.

Comparative Example 1

Another quarter-cylindrical molded article having a weight of 15 25 mg was prepared according to the same procedures as in Example 2 except that no HCO-60 was added.

Example 2

The molded articles of Example 1 and Comparative Example 1 were each used as they were to conduct elution tests. Each article was 20 put into physiological saline containing 0.5% Tween 80, and 1 to 3 ml

of the solution was directly sampled at the time of measurement, and measured for its absorbance at 210 nm. The relationship between elapsed time and percent release calculated from the absorbance obtained above is shown in Fig. 1.

5 Reference Example 1

The implantable sustained release preparations obtained in Example 1 and Comparative Example 1 were each used to examine their effect on graft survival period after heart transplantation in rats. Ten Wister rats were divided into two groups (each consisting of 5 animals), 10 and hearts from Buffalo rats were heterotopically transplanted into abdominal cavities of all Wister rats. Each group was then received the following treatments:

Group 1: The implant of Comparative Example 1 was fixed with a surgical suture in such a way that the drug was brought into intimate 15 contact with the thymus. Simultaneously, 5 mg/kg cyclosporin A was intravenously injected.

Group 2: The implant of Example 1 was fixed with a surgical suture in such a way that the drug was brought into intimate contact with the thymus. Simultaneously, 5 mg/kg cyclosporin A was intravenously 20 injected.

For each group, the graft survival periods were determined, and the results are shown in Table 1.

Table 1

Rat Group	Graft Survival Period (days)	Average Graft Survival Period (days)
1	7, 7, 7, 8, 9	7.6 ± 0.9
2	10, 16, 21, 22, 36	21.0 ± 9.6

As apparent from the above results, when the preparation of 5 Comparative Example 1 employing no HCO-60 was used, the graft survival period (in days) was short because release of cyclosporin A was not accelerated and therefore immunological functions were not suppressed. On the contrary, the preparation of the present invention employing HCO-60 improved the sustained release profile of 10 cyclosporin A as shown in Fig. 1, and thereby prolonged the graft survival period (in days) remarkably.

OPERATION AND EFFECT OF THE INVENTION

In an implantable sustained release immunosuppressive drug of the present invention comprising a bioabsorbable aliphatic polyester, 15 a nonionic surfactant, and a fat-soluble immunosuppressive agent, the nonionic surfactant added to the bioabsorbable aliphatic polyester forms a matrix containing the immunosuppressive agent dissolved therein and thereby prevents precipitation of the agent during

preparation. Such matrix in which the agent is homogeneously dissolved allows the immunosuppressive agent in the sustained release preparation to be efficiently transferred into the lymph duct according to a desired sustained release profile, when molded into an implantable 5 shape which allows intimate contact with an organ in the lymphatic system, especially thymus, and implanted in such a manner that it is brought into intimate contact with the organ in the lymphatic system.

By appropriately selecting the type and the ratio of the nonionic surfactant used in the sustained release preparation, the 10 duration of sustained release and the amount of sustained release, that is, the sustained release rate may be controlled as desired, and the sustained release properties of the drug can be properly regulated with the cooperation of the sustained release capability of the bioabsorbable polyester itself. In addition, the nonionic surfactant also produces, 15 after sustained release of the agent, an absorption promoting effect so that the agent may easily permeate into thymus and lymphatic glands to keep the concentration at the site of action constant, thereby allowing the immunosuppressive agent to properly maintain and sufficiently produce its pharmacological effects in the lymph duct. Furthermore, 20 by using an implantable sustained-release immunosuppressive drug of

the present invention, one may reduce myelosuppression and/or renal dysfunction associated with such medications as compared with conventional methods by injection or oral administration. Moreover, since bioabsorbable aliphatic polyesters undergo hydrolysis, they will 5 not remain in the body without the need of removing them out of the body. Thus, sustained release preparations of the present invention will greatly contribute to the medical field.

BRIEF DESCRIPTION OF DRAWING

Fig. 1 shows the relationship between percent release of 10 cyclosporin A and elapsed time for the sustained release preparation obtained in Example 1 which contains cyclosporin A.